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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,762	09/05/2003	Charles R. Cantor	701586-053023	6905

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/655,762	CANTOR ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 10-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on June 30, 2010.

Preliminary Remark

Claims 4-9, 14, and 15 are canceled.

Claims 1-3 and 10-13 are pending and are under prosecution herein.

Upon final searching of the application prior to allowance, a new prior art of material had been discovered. Accordingly, the present Office Action contains at least one rejection, not necessitated by Applicants' claim amendment, resulting in said Office Action being made **Non-Final**.

Claim Rejections - 35 USC § 112

The rejection of claim 15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on April 13, 2010 is withdrawn in view of the Amendment received on June 30, 2010, canceling the rejected claim.

Claim Rejections - 35 USC § 103

Rejection, New Grounds

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pannetier et al. (U.S. Patent No. 5,747,246, issued May 5, 1998, filed June 21, 1994) in view of

Amexis et al. (PNAS, October 2001, vol. 98, no. 21, pages 12097-12102) and Ross et al. (BioTechniques, September 2000, vol. 29, pages 620-629)[1].

With regard to claim 1, Pennetier et al. disclose a method of quantifying the absolute amount of at least two target nucleic acid sequences corresponding to at least two genes in a biological sample, comprising the steps of:

(a) preparing a sample by combining in a sample the biological comprising the at least two target nucleic acid sequences corresponding to the at least two genes and a known amount of at least two standard nucleic acids ("[t]he subject of the present invention is also a process according to one of the preceding embodiments for multiparametric analysis, enabling several DNA fragments of interest to be assayed and quantified in the same sample under analysis, characterized in that: to the sample to the to be analyzed containing said DNA fragments of interest, an equal number of standard DNA fragments are added, the standard DNA fragments being different for each of the DNA fragments of interest, and the standard DNAs and the labeled oligonucleotides of step 3) are chosen in such a way as to generate fragments of different sizes during step 3)", column 9, lines 13-25), wherein said at least two standard nucleic acids have a nucleotide sequence that is one base different than the respective target nucleic acid sequence ("[p]referably, the sizes of DNA fragment of interest and the standard fragment differ by at least one nucleotide and by not more than approximately 10% of nucleotides per strand, or by 1 to 5 nucleotides," column 6, lines 37-41; "[a]ccording to the invention, the DNA fragment of interest and the standard fragment are as similar in length and sequence as possible. Preferably, the standard fragment carries as minor a modification as possible relative to the DNA of interest, and differs in at least one site which can be

[1] This rejection was already made in the Final Rejection mailed on November 21, 2007, wherein Ross et al. reference was cited as an evidentiary reference for Official Notice taken. The Final Rejection under this practice was justified as set

identified by some appropriate means. This ensures a greater similarity in their level of amplification, which is a major factor for the accuracy and reliability of the method for reproduction from sample to sample", column 6, lines 16-23);

(b) amplifying the sample of step (a), "((2) the DNA fragment of interest and the standard fragment are coamplified with the same oligonucleotide primers, preferably to saturation of the amplification of the DNA fragment of interest or in the last cycles prior to saturation", column 4, bottom to column 5, line 36);

(c) using a single subsequent amplification method at the site of differentiation to enhance the difference between the at least two standard nucleic acid seuqences and the at least two target nucleic acid sequences corresponding to the at least two genes at the site wherein each of the standard nucleic acid sequence differs from the respective target nucleic acid sequence corresponding to the at least two genes ("(3) one or more labeled oligonucleotide primer(s), specific for the DNA fragment of interest and the standard fragment and different from the amplification of oligonucleotide primers of step 2), is/are added to the reaction medium obtained in step 2), and one or more additional amplification cycle(s) with said primer(s) is/are performed with a DNA polymerase, so that during a cycle, after denaturation of the DNA, said labeled oligonucleotide primer(s) hybridize(s) with said fragments at a suitable site in order that an elongation with the DNA polymerase generates labeled DNA fragments of different sizes and/or sequences and/or with different labels according to whether they originate from the DNA fragment of interest or the standard fragment, respectively", column 4, bottom to column 5, line 36);

(d) detecting and quantifying the enhanced products ("(4) the initial quantity of DNA fragment of interest is determined as being the product of the initial quantity of standard DNA

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forth in MPEP 2144.03(D). The Ross reference is now being cited as a part of the references being relied upon in the

fragment and the ratio of the quantity of amplified DNA fragment of interest to the quantity of amplified standard DNA fragment, which ratio is identical to that of the quantities of the labeled DNA fragments originating from the amplified DNA fragment of interest and the amplified standard fragment, respectively, obtained in step 3)", column 4, bottom to column 5, line 36).

Regarding claim 3, the target nucleic acid is mRNA ("In this example, the concentration of the messenger RNAs resulting from the transcription of class I genes of the major histocompatibility complex of the mouse is measured in different organs…" (column 10, lines 39-42).

Regarding claims 10-13, Pannetier et al. disclose that at 50 genes can be quantified with corresponding 50 respective standard nucleic acids ("It is then possible, in a single size determination, to assay and quantify up to 50 genes in the same sample." (column 9, lines 1-13)

Pannetier et al. do not employ mass spectrometry in their quantification method.

Pannetier et al. do not explicitly disclose that target nucleic acids are from an infectious agent (claim 2).

Amexis et al. disclose a method of quantifying a target nucleic acid in a sample, in particular, RNA virus (thus infectious agent), wherein the method comprises the steps of:

a) amplification of a target nucleic acid with a pair of primers (Figure 1B; page 12098, 2nd column, 3rd paragraph);

b) amplifying the amplified product with MassExtend primers which is specific for a point mutation (Figure 1B; page 12098, 2nd column, 3rd paragraph (middle)); and

c) detecting and quantifying the amplified products (Figure 1B; page 12098, 2nd column, 3rd paragraph (bottom); Abstract; page 12098, 1st column, 3rd paragraph).

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present rejection.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Pannetier et al. and with the teachings of Amexis et al., thereby arriving at the claimed invention for the following reasons.

The method employed by Pannetier et al., which is drawn to the amplifying the target nucleic acid and the standard nucleic acid (which embraces a single nucleotide mutation) via use of primers which flank the target nucleic acid region, employs more than a decade old technique – that is – restriction digest, electorphoresis, followed by the labeled quantitation method.

Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to employ a more sophisticated method of accurately quantitating the target nucleic acid, such as MALDI-TOF, thereby arriving at the claimed invention.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at combining the teachings since methods of quantification employing mass spectrometry, such as SNuPE (single nucleotide primer extension), have been well-established.

For example, multiplex detection of different target nucleic acids (i.e., different markers) via MALDI-TOF was known prior to Applicants' filing of the application.

> "A main advantage of MALDI-TOF MS-based genotyping is its ability to multiplex many primer extension assays within a single sample…Multiplex PCR and primer extension assays were performed for the CP450 polymorphism and a polymorphism in human LDLR region by amplifying homozygote and heterozygote samples. Multiplex PCR products from heterozygous mutant and homozygote samples were combined … and the mixture was genotyped. The data show unambiguous detection of the low-abundance alleles for both loci tested. A quantitation study was not performed for the multiplex experiments; however, the data are presented here to provide a basis for future investigation." (page 625, Ross et al., "Quantitative Approach to Single-Nucleotide Polymorphism Analysis Using MALDI-TOF Mass Spectrometry," BioTechniques, September 2000, vol. 29, pages 620-629)

Given the fact that Amexis et al. amplify a known target nucleic acid sequence via use of a flanking primer pairs, followed by the mutation-specific primer extension, one of ordinary skill in the art would have recognized that the amplification products of Pannetier et al., would have served equally well for the mutation-specific primer extension, which would have been necessary for the subsequent mass spectrometric analysis.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Double Patenting

The rejection of claims 1-3 and 10-13 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/589,709 (herein, the '709 application), made in the Office Action mailed on April 13, 2010 is withdrawn in view of the Terminal Disclaimer received on June 30, 2010.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 6:00 a.m. to 2:30 p.m (M-F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
Primary Examiner
Art Unit 1637
9/15/2010

/YJK/